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Frequency and patterns of MRI abnormalities due to status epilepticus

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ABSTRACT

Background: MRI changes due to status epilepticus (SE) often suggest a combination of cytotoxic and vasogenic edema, but it is unclear why only certain patients have MRI changes.
Objectives: To determine the frequency of MRI changes due to SE and the associated patient characteristics.
Methods: We reviewed records for demographics, medical history, and MRI changes attributable to seizures of all patients admitted to Brigham and Women's Hospital or Massachusetts General Hospital for SE from 1/1999 to 7/2003 and who had MRI during admission.
Results: Ten (11.6%) of the eighty-six patients identified had MRI abnormalities likely due to seizures. Four, two with pre-existing epilepsy and two with extratemporal structural lesions, had focally increased signal on T2 and diffusion-weighted imaging (DWI) in the hippocampus ipsilateral to the seizure focus. One, with elevated levels of clozapine, had increased signal on T2 weighted images and variably restricted diffusion in the splenium. Five had gyral distribution of restricted diffusion and increased signal on T2 weighted images; they had complex medical comorbidities and possible hypoperfusion or hypoxia associated with SE.
Conclusions: Among patients with SE who had MRI changes, those with previous epilepsy or extratemporal structural lesions showed increased diffusion in the hippocampus and may have selective hippocampal vulnerability to seizure-induced hyperexcitability. Patients with hyperintense signal in the cortical gray matter had episodes of possible hypoperfusion or hypoxia.

1. Introduction

Visible cerebral changes, notably increased blood flow, due to seizure activity were first described by Horsley in 1892: "I had the opportunity of witnessing an epileptic fit in a patient at the time of an operation in which the "motor" region, so-called, was exposed and electrically stimulated. In that case, the cortex was ... distinctly hyperaemic during the attack."[1] Reversible hyperperfusion and mild edema have also been noted with acute seizures during angiography[2] transient hypodensities were noted on early CT,[3] and the first MRI report was in 1986,[4] with reversible findings noted in 1987.[5] Since then there have been many case reports, small series, and animal studies showing reversible and irreversible MRI findings. In addition to localized hyperperfusion, reported changes include contrast enhancement, increased T2 fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) signal, and a variable degree of reduction in the apparent diffusion coefficient (ADC).[5–9] The imaging findings associated with SE may reflect the many physiologic changes that can occur during SE, including cerebral edema, hyperperfusion, and alteration of the blood–brain barrier.

The prevalence of these changes after either SE or isolated seizures is unknown. The aim of this study is to explore the frequency, imaging characteristics, and clinical correlates of MRI changes attributable to SE.

2. Materials and methods

Adults admitted with a diagnosis of SE or seizure to Brigham and Women's Hospital or Massachusetts General Hospital from January 1999 to July 2003, and who had undergone brain MRI during their hospitalization were identified through a research patient data registry. Patients with SE due to hypertensive encephalopathy, eclampsia, or acute encephalitis were excluded. A diagnosis of SE was met if the seizure lasted longer than 30 min or if the patient had intermittent seizure activity for longer than 30 min without regaining baseline function. Charts of all patients meeting the above criteria were reviewed for clinical data

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including age, sex, diagnoses, history of epilepsy, timing of initial and follow-up MR imaging, and EEG findings. Permission for this search and chart review was obtained from the Institutional Review Board.

If an MRI abnormality was reported as possibly due to seizures, a neuroradiologist (AZ) visually reviewed the images; no volumetric measurements were performed. MRI abnormalities were attributed to SE if they did not appear to represent strokes or tumors, and their location corresponded to the EEG abnormality or seizure semiology.

MR imaging was performed with a Signal 1.5-T system (GE Medical Systems, Milwaukee, WI). Sagittal and transverse T1-weighted images (repetition time, 600 ms; echo time 25 ms), FLAIR (repetition time, 6000–10,000 ms; echo time, 120–141 ms; inversion time, 2000–2200 ms) and transverse T2-weighted images (repetition time, 3000–4450 ms; echo time, 102–105 ms; EC = 1) were acquired with 5-mm contiguous sections. 78/86 patients (91%) of patients received DWI as well. Acquisition parameters for DWI included repetition time of 6000–10,000 ms, echo time of 80–154 ms, and a maximum b value of 1221 s/mm^2. Statistical analyses were performed using Fisher's exact test.

3. Results

Sixteen of eighty-six patients had MRI reports listing seizures as a possible cause of MRI abnormalities. Six were excluded, one due to an acute stroke, one due to a tumor near the region of interest and 4 because of suspected encephalitis. The remaining 10 (11.6%) were identified as having MRI changes attributable to SE. Patients with and without such changes did not differ with regard to age, sex, etiology of SE, history of epilepsy, or time to MRI (Table 1). In the other 76 patients, 64 (84.2%) showed abnormalities. Ischemic stroke was the most common finding in 11 (14.5%), followed by tumor in 10 (13.2%), chronic stroke in 10 (13.2%), nonspecific white matter changes in 8 (10.5%), possible encephalitis in 7 (9.2%), anoxic changes in 5 (6.6%), intracerebral hemorrhage, vascular malformations, old contusions and multiple sclerosis in two each (2.6%), and possible hypertensive leukoencephalopathy, agenesis of the corpus callosum, sarcoidosis, abscess, and diffuse atrophy in one patient each (1.3%).

Five of the ten patients had a history of epilepsy. Of the remaining 5, 2 developed epilepsy, 1 died, and the other 3 were lost to follow-up. All had focal seizures, 3 with left, 5 with right, and 2 with bihemispheric onset; 4 had secondary generalization. Ictal EEGs were obtained in 7; in the other 3, seizures were observed clinically, while EEG performed the same day showed periodic lateralized epileptiform discharges (PLEDs) in 2, and postictal focal slowing in one whose EEG was performed 2 days later (Table 2). Of these 10 patients, 3 required pharmacologically induced coma to treat SE (patients 2, 3 and 9). Initial MRI was performed in <24 h in 5 and up to 11 days after onset in the others. Follow-up MRI was obtained for the nine surviving patients.

Three patterns of MRI change were identified (Fig. 1, Table 3). The first consisted of increased DWI signal in the hippocampus ipsilateral to the side of seizure onset (patients 1, 6, 7, and 10). One patient also had T2 prolongation in the ipsilateral insula and posterior thalamus (patient 10). Three had reduced intensity in the hippocampus on ADC mapping, consistent with restricted diffusion. Three of these patients had previously diagnosed epilepsy, two with extratemporal vascular malformations and one with hippocampal sclerosis. The other patient later developed epilepsy and mesial temporal sclerosis (patient 7).

The second pattern was a gyral distribution of restricted diffusion and T2 prolongation, seen in five patients (2, 3, 5, 8, and 9). Changes were also seen in the ipsilateral posterior thalamus (patients 2, 3, 8 and 9) and the contralateral cerebellum (patient 8); all 3 with ADC mapping had reduced cortical signal. All 5 had possible hypoperfusion and/or hypoxia–ischemia associated with SE (2 with acute myocardial infarction, 1 episodic hypotension, 1 episodic hypoxia, and 1 ipsilateral subclavian steal syndrome), compared to one of the patients with other patterns of MRI change ($p = 0.05$) and 22/54 without MRI change due to SE ($p = 0.28$). Three patients showed improvement on follow-up imaging.

The third pattern seen was of restricted diffusion in the splenium. This patient had elevated levels of clozapine and bitemporal SE. MRI became normal after the patient discontinued clozapine and started treatment with antiepileptic drugs.

4. Comment

MRI findings attributable to SE may provide insight into the mechanism of SE and associated neuronal damage. The hippocampal pattern has been reported previously [10–12] rarely with extratemporal epilepsy.[13–15] This is the change most frequently

Table 1
Characteristics of all patients and patients with changes on MRI due to status epilepticus

Characteristic	Patients without changes	Patients with changes
Total number	76	10
Demographics		
Sex, M	36	5
Sex, F	40	5
Mean age (range)	52 (19–86)	44 (22–83)
Hx of epilepsy	22	5
Mean days from onset until MRI	3.50	3.49
Primary etiology		
Vascular	15	2
Low AED level	12	3
Tumor	10	0
Unknown	6	2
Infection	8	[a]
ETOH/benzodiazepine withdrawal	8	0
Epilepsy (with no provoking factors identified)	6	1
Toxic–metabolic	3	2
Anoxia	5	[a]
MS	0	1
Mitochondrial	2	[a]

[a] Changes seen could not be definitively attributed to seizures *P*-value >0.05 for all comparisons.

Table 2
Characteristics of patients with MRI findings due to status epilepticus

	Age (year)/sex	Seizure type	Duration	EEG	Etiology/relevant history
1[a]	52/F	SPS (aphasia) and CPS	1 day	Left temporal lobe seizures	Low AED level, History of occipital AVM resection
2	41/F	CPS with secondary generalization	21 days	Posterior quadrant seizures, bilateral independent	Vascular
3	22/M	CPS with secondary generalization	54 day	Left hemisphere seizures	Unknown (drug and/or alcohol abuse suspected)
4	42/F	CPS	>1 day (overall duration unknown)	Bitemporal seizures	Toxic–metabolic, bipolar disorder; EEG performed to evaluated subacute change in mental status
5	52/M	SPS (R motor)	1 day	Post-ictal left hemisphere slowing	Unknown—in the next month developed subclavian stenosis
6[a]	55/M	SPS (R motor) with secondary generalization	4 days	R hemisphere seizures and PLEDs	Cavernous angioma with intractable epilepsy
7[a]	45/M	GTC	<1 day	R PLEDs	No acute precipitant; history of multiple sclerosis
8[a]	36/M	GTC	<1 day	R hemisphere seizures	Low AED levels
9	83/F	L motor with secondary generalization	2–4 days	R PLEDs	Unknown; found unresponsive and last seen 2 days prior; hypercalcemic
10[a]	44/F	CPS	4 days	R frontal seizures	Diabetes with acute hypoglycemia and history of epilepsy

CPS: complex partial seizure; GTC: generalized tonic clonic; SPS: simple partial seizure; AED: antiepileptic drug; HC: hippocampus; PLEDs: periodic lateralized epileptiform discharges.
[a] Epilepsy prior to SE.

seen in animal models of SE.[16] In humans, after prolonged nonfebrile or febrile seizures, the hippocampus can initially become enlarged and hyperintense, and later atrophy. Neuropathological examination can show hippocampal sclerosis,[17] The hippocampal abnormalities may reflect the vulnerability of the hippocampus to excitotoxic damage, or to immediate or delayed neuronal death through necrosis and apoptosis.[18]

The cortical MRI pattern was seen in patients with possible hypoperfusion or hypoxia. Focal SE has previously been shown to produce MRI changes in the neocortical region corresponding to

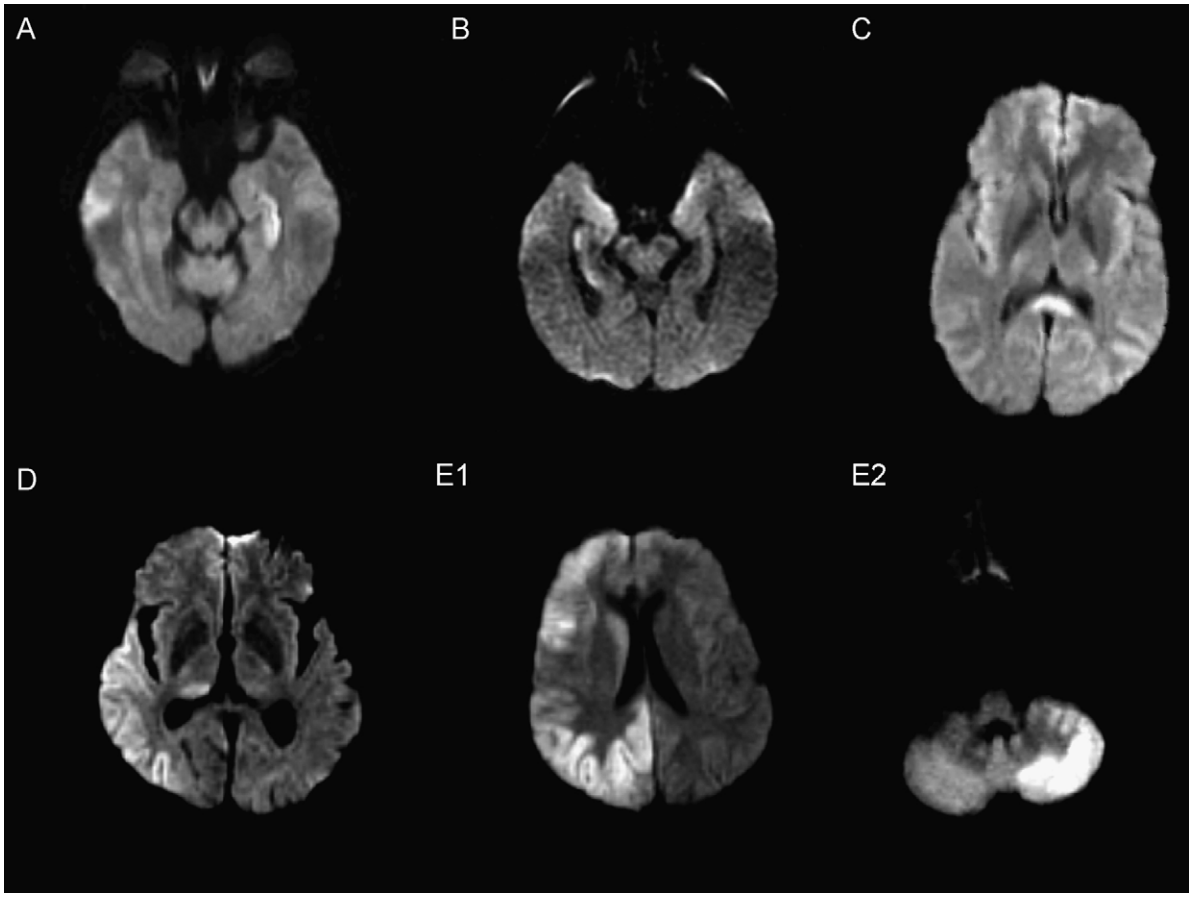

Fig. 1. (A) Axial DWI during episode of focal SE in a 52-year-old woman with history of left occipital AVM resection and epilepsy who presented with episodic aphasia and confusion. There is restricted diffusion in the left hippocampus. (B) Axial DWI during focal motor SE showing restricted diffusion in the right hippocampus in a 55-year-old man with a right parietal cavernous angioma and medically intractable epilepsy. (C) Axial DWI showing expanded and hyper-intense splenium in a 52-year-old woman during SE characterized by bitemporal seizures and change in mental status. (D) Axial DWI showing gyral pattern of restricted diffusion and ipsilateral thalamic change in an 83-year-old woman with left hemisphere seizures and hypotension. (E) Axial DWI images showing E1 gyral pattern of restricted diffusion and E2 crossed cerebellar diaschisis in a 36-year-old man with epilepsy who presented with hypoxia and recurrent right hemisphere SE.

Table 3
MRI findings

	Initial MRI								Follow-up MRI		
	Timing	DWI hyperintensity	ADC signal	Area of increased T2 signal					Timing	DWI	T2
				Hippocampus	Neocortical gray matter	Thalamus	Cerebellum	Other			
1	<24 h	Yes	↓	Left					2 weeks	Slight hyperintensity	Slight hyperintensity
									1 month	N	N
2	<24 h	Not performed	Not performed		Bilateral frontal and insula, left parietal, right cingulate	Bilateral posterior			2 weeks		Less hyperintense in cortical regions, thalamus unchanged
3	11 days	Yes	↓		Bilateral diffuse	Bilateral posterior			6 months	N	N
4	UK[a]	Yes	↓					Splenium	10 weeks	N	N
5	2 days	Yes	Not performed		Left insula and cortex				1 week		Less hyperintense
6	1 day	Yes	↓	Right			Left		1 year		Hippocampal sclerosis
7	1 day	Yes	↓	Right					1 year		Hippocampal sclerosis, left cerebellar stroke
8	<12 h	Yes	↓		Right diffuse	Right	Left	Right caudate	Not performed		
9	1 day	Yes	↓ (except thalamus)		Bilateral occipital, R temporal	Right posterior			3 days	ADC increased	Unchanged
10	8 days	Yes	← ↑	Right	Right insula	Right posterior			1 week	Less hyperintense	Increased + increased signal in left cerebellum

[a] UK, unknown, several MRIs were obtained with the same finding prior to EEG and change in treatment.

the zone of seizure onset, with reversible diffusion as well as perfusion changes in nonconvulsive SE.[19–21] In some cases, focal atrophy results.[22] Signal changes were seen not only in the areas primarily involved in seizure activity but also in those remote from but functionally connected to the epileptogenic cortex, including the ipsilateral posterior thalamus (patients 2,3, 8, 9, and 10) and contralateral cerebellum (patient 8, patient 6 had a contralateral cerebellar stroke and patient 10 had contralateral cerebellar changes on repeat imaging). Similar thalamic changes have been seen in animal models[23] and case reports,[21,24] though the specific involved nuclei have not been determined; contralateral cerebellar changes are more easily explained by known corticocerebellar connections.[21] This pattern may be associated with reduced energy supply.

With either the cortical or hippocampal pattern, increased DWI and decreased ADC signal may represent cytotoxic edema, and T2 prolongation and increased signal on DWI without decreased ADC may represent vasogenic edema. Laminar necrosis from the original injury is possible, but seems unlikely in that changes were reversible among those imaged a week or more later. On the other hand, the same characteristics that predispose these neuronal populations to necrosis may predispose them to the temporary supply-demand mismatch caused by SE. These two processes raise the possibility of developing neuroprotective strategies that target excitotoxic and substrate mismatch mechanisms similar to those being investigated in neuroprotection after stroke. With further understanding of the MRI changes induced by seizures, MRI could be used as a surrogate marker for evaluating potentially neuroprotective agents and strategies. The third pattern, that of signal increase in the splenium, has been reported in various situations, including bitemporal seizures,[27] antiepileptic drug withdrawal,[28] and osmotic or metabolic injury of various types.[29,30] This lesion may represent a different and as yet undefined mechanism of seizure-induced injury. In patient 4, elevated levels of clozapine may have contributed, presumably by causing SE, but direct neurotoxic effects cannot be ruled out. The splenium may be particularly visible on DWI because of a high myelin water fraction (believed to represent water trapped between the lipid bilayers), making DWI of the splenium particularly sensitive for restricted free water motion in toxic–metabolic conditions and states of excitotoxicity such as SE.

Limitations of this study include variability in the timing and sequence of initial and follow-up MRI and in clinical follow-up. Also, some patients admitted in SE, primarily those with known epilepsy, did not receive MR imaging; therefore, the overall frequency of MR changes may be underestimated. Although our reliance on the formal MRI report to screen studies for detailed review could also have resulted in missing some patients whose images showed subtle seizure-induced changes, the neuroradiologists at our institutions were well aware of such changes, particularly those that were not explained by the clinical history apart from SE. The frequency of MRI abnormalities was similar to a pediatric series.[31] However that study did not specifically mention any abnormalities due to SE alone. As seen in Table 1, we could not find any clinical variables that reliably distinguished patients with MRI changes from those without. However, variability in mitochondrial reserve, presumably on a genetic basis, might explain these differences.

In summary, we found MRI changes attributable to SE in 11.6% of cases, and these changes seemed to correlate with seizure localization and underlying pathology. The differences in the observed MRI patterns and their clinical correlates may provide insight into the mechanisms of SE-related neuronal injury and suggest means of targeting neuroprotective strategies.

Conflicts of interest

The authors have reported no conflicts of interest.

Competing interests

The authors have no competing interests.

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